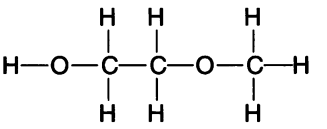
Comparison of Reproductive Responses of Different Strains (3 Studies)–II

Ethylene Glycol Monomethyl Ether



CAS #109-86-4
C57BL/6 mice, at 0.0, 0.03, 0.1, 0.3%, drinking water
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Ethylene glycol monomethyl ether (EGME), a common chemical and solvent used in industry and in consumer goods, was used to test the hypothesis that mouse strains of differing basal fertility would respond differently to a reproductive toxicant (Chapin et al., Fundam Appl Toxicol 21:8–14 [1993]). This study used C57Bl/6 mice in a modified RACB protocol. The design was modified to use 30 pairs of mice per group instead of the usual 40 per control and 20 per treated group. Neither Task 3, the crossover mating test, nor Task 1, normally used to set doses for the continuous cohabitation phase, were conducted, because sufficient data were already available on affected sex and the optimal doses to use. In all three studies, dose levels of EGME in drinking water for Task 2 were set at 0.03, 0.1, and 0.3% EGME, weight per volume. These concentrations produced estimated consumption values of approximately 50, 170, and 500 mg/kg/day. Water consumption was not reduced by addition of EGME. One male and two females died in the control group during Task 2, and one male, one female, and two males died in the low to high dose groups, respectively. These deaths were judged not to be treatment related.

While 23 of 27 control pairs delivered any pups, only 7 of 28 high dose pairs had any pups. Of those, five pairs delivered only one litter, and no high dose pair delivered more than two litters. Thus, the mean number of litters per fertile pair declined from 3.57 (control) to 1.29 (high dose). Additionally, there were no live pups ever delivered at the high dose. The mean number of live pups per litter declined at the middle dose, from a control value of 8.0 to 6.9. A greater proportion of pups were born dead in the middle dose group (18% vs a control value of 8%). The mean pup weight adjusted for litter size increased at the low and middle doses by approximately 2 and 4%, respectively.

The pups from the last litter were reared by their dam until weaning. In control litters, 75 and 87% of male and female pups, respectively, survived until weaning. In the middle dose group, these values were reduced to 33 and 28%, respectively. Absolute female pup weight was reduced only at weaning by approximately 35%; male pup weight was not significantly decreased.

After weaning the F_1 mice, all remaining F_0 mice were killed and necropsied. There were no changes in female body or organ weights. Male mice in the high dose group weighed 10% less than controls, and the adjusted liver weight for the middle dose males was increased by approximately 6%. At the high dose, absolute testis weight was decreased by approximately 30%, relative epididymis weight was decreased by approximately 11%, the percent motile epididymal sperm and epididymal sperm density were decreased by approximately 30 and approximately 34%, respectively. The percentage of abnormal sperm was increased at the middle and high doses, from a control value of 29 to 37 and 96% abnormally formed sperm, respectively.

At 74 ± 10 days of age, F_1 mice were cohabited for a week within treatment groups. While there were sufficient F_1s to make 20 non-sib pairs in the control and low dose groups, there were sufficient middle dose animals to form only six breeding pairs. Five of those six mated, but none delivered a litter of live pups (vs 14/20 that delivered live young in the control group). Thus, F_2 pups were available from only the low dose group and the controls. There were no differences between these groups in pup weight, mean pup number, viability, or proportion of males.

After the F_2 pups were delivered and assessed, all mice were killed, and the F_1 mice were necropsied. While there was no effect on female body weight, there was a 50% reduction in ovary weight at the middle dose (n=6), and a 26% increase in adjusted kidney weight. In males, there were no changes in body weight, while middle dose males showed a 25% increase in relative kidney weight and a 34% reduction in prostate weight. Seminal vesicle weight was reduced in the low and middle dose groups by 6 and 15%. Abnormal sperm forms were increased in the middle dose group, from a control value of 25%, to a treated value of 43% abnormal. Epididymal sperm density in the low dose was reduced by 11%; the 23% reduction in the middle dose group was not significant due to the small number of mice.

In summary, this strain had fewer pups per litter, and fewer litters per pair overall compared to the Swiss CD-1 strain, but more than the C3H strain. EGME completely inhibited successful reproduction at the top dose. The middle dose level (0.1%) was toxic, based on reductions in pup number and increases in abnormal sperm forms. In this strain, the low dose produced adverse effects in the second generation (reduced seminal vesicle weight and epididymal sperm count) that were not seen with the other strains at this dose. Compared to the Swiss CD-1 mice, C57s had lower basal fertility, and were more affected by EGME exposure. This supports the hypothesis that strains of lower basal fecundity evidence greater reproductive toxicity than more robust and fertile strains when challenged with a toxicant.

Summary: NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: **PB89152565/AS**
Chemical: **Ethylene Glycol Monomethyl Ether**
CAS#: **109-86-4**
Mode of exposure: **Drinking water**
Species/strain: **C57BL/6 mice**

F_0 generation — Dose concentration →	0.03%	0.1%	0.3%
General toxicity	Male, female	Male, female	Male, female
Body weight	—, —	—, —	↓, —
Kidney weight[a]	—, —	—, —	—, —
Liver weight[a]	—, —	↑, —	—, —
Mortality	—, —	—, —	—, —
Feed consumption	•, •	•, •	•, •
Water consumption	—, —	—, —	—, —
Clinical signs	—, —	—, —	—, —
Reproductive toxicity			
x̄ litters/pair	—	—	↓
# live pups/litter; pup wt./litter	—, —	↓, ↑	•, •
Cumulative days to litter	—	—	↑
Absolute testis, epididymis weight[a]	—, —	—, —	↓, ↓
Sex accessory gland weight[a] (prostate, seminal vesicle)	—, —	—, —	—, —
Epidid. sperm parameters (#, motility, morphology)	—, —, —	—, —, ↑	↓, ↓, ↑
Estrous cycle length	•	•	•

Determination of affected sex (crossover)	Male	Female	Both
Dose level	•	•	•

F_1 generation — Dose concentration →	0.03%	0.1%	•
General toxicity	Male, female	Male, female	Male, female
Pup growth to weaning	—, —	—, ↓	•
Mortality	—, —	—, —	•
Adult body weight	—, —	—, —	•
Kidney weight[a]	—, —	↑, ↑	•
Liver weight[a]	—, —	—, —	•
Feed consumption	•	•	•
Water consumption	↓, ↓	↓, ↓	•
Clinical signs	—, —	—, —	—, —
Reproductive toxicity			
Fertility index	—	↓	•
# live pups/litter; pup wt./litter	—, —	•, •	•, •
Absolute testis, epididymis weight[a]	—, —	—, —	•, •
Sex accessory gland weight[a] (prostate, seminal vesicle)	—, ↓	↓, ↓	•, •
Epidid. sperm parameters (#, motility, morphology)	↓, —, —	—, —, ↑	•, •, •
Estrous cycle length	•	•	•

Summary information	
Affected sex?	Unclear
Study confounders:	None
F_1 more sensitive than F_0?	Yes
Postnatal toxicity:	Yes

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change ($p<0.05$); —, —, no change in males or females. [a]Adjusted for body weight.